Metastatic renal cell carcinoma to the small bowel: three cases of GI bleeding and a literature review

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Abstract

Approximately 25–30% of patients with renal cell carcinoma (RCC) have metastatic disease at the time of diagnosis, where the most common sites of metastasis are the lung (50–60% of patients with metastatic disease), bones (30–40%), liver (30–40%), and brain (5%). Although RCC metastasis to the small intestine is thought to be exceedingly rare, with predominantly isolated case reports and a few case series in the literature, we present below three additional cases at our institution of metastatic RCC to the small bowel presenting as GI bleeding. A literature review demonstrates that the number of published case reports has been increasing in recent years. We hypothesize that in the era of targeted chemotherapy and VEGF inhibitors to treat RCC that patients are living longer and have more time for their primary tumors to metastasize to the small bowel and become symptomatic, causing metastatic RCC to the small bowel to be less rare than previously thought.

Keywords Renal cell carcinoma · Small bowel metastasis · Upper GI bleed

Introduction

Approximately 25–30% of patients with renal cell carcinoma (RCC) have metastatic disease at the time of diagnosis [1]. The most common sites of RCC metastasis are the lung (50–60% of patients with metastatic disease), bones (30–40%), liver (30–40%), and brain (5%) [1]. Although RCC metastasis to the small intestine is thought to be exceedingly rare, with predominantly isolated case reports and a few case series in the literature [2–6], since 2015, there have been 11 different case reports or series published in the literature. We present herein three additional cases of metastatic RCC to the small intestine seen recently at our institution as well as a brief literature review.

Case series

Case 1

A 48-year-old man presented to our Emergency Department with a 6-day history of melena and lightheadedness and a 1-day history of bright red blood per rectum. He had a history of metastatic RCC to the bones, adrenal gland, and lungs diagnosed 7 months prior, and he had been treated with a laparoscopic right radical nephrectomy. The pathology of the nephrectomy specimen showed a clear cell RCC with extensive sarcomatoid features. He was then started on sunitinib, which inhibits cellular signaling by targeting multiple receptor tyrosine kinases, including vascular endothelial growth factor receptors. Unfortunately, this medication was stopped 2 months later when he suffered a non-ST segment elevation myocardial infarction, at which point he was started on dual antiplatelet therapy.

Upon presentation, he endorsed mild nausea, a single episode of emesis, and a decreased appetite. Laboratory studies revealed a hemoglobin level of 7.8 g/dL and a hematocrit level of 23.2%. Esophagogastroduodenoscopy revealed no pathology. A colonoscopy demonstrated old blood throughout the colon and fresh blood in the terminal ileum but identified no specific source of bleeding. His hematocrit level did not stabilize after 4 units of packed red

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Fig. 1 Radionuclide-tagged red blood cell study demonstrating a small focus of radiotracer extravasation in the right lower quadrant

Fig. 2 Mesenteric angiogram demonstrating an ovoid, hyper-enhancing lesion in the right lower quadrant, likely in the small bowel, supplied by branches of the ileocolic artery

blood cells were transfused. Three days after admission, a video capsule enterography was performed that demonstrated erythematous gastropathy and a cratered ulcer in the mid-ileum. A nuclear medicine-tagged red blood cell (RBC) scan (Fig. 1) as well as conventional angiography (Fig. 2)

were performed. An actively bleeding mass was identified in the ileum. Embolization of branches of the ileocolic artery was performed, but given the high risk of re-bleeding, he was taken to the operating room for surgical resection of the intestinal metastasis.

Via a small midline laparotomy, we eviscerated the small bowel and readily identified a 1.5-cm, discoid-shaped tumor within the wall of the ileum, approximately 50 cm proximal to the ileocecal valve. We resected the short segment of small bowel and performed a stapled, side-to-side anastomosis. His post-operative course was uncomplicated, and he was discharged to home on post-operative day 3. Final pathology demonstrated a 2.1×1.6 -cm tan-brown, ovoid, raised mucosal mass that invaded through the small bowel muscularis and abutted the serosa, consistent with metastatic RCC. He had no further gastrointestinal (GI) bleeding. Systemic therapy was never resumed after surgery, though he did receive palliative radiation therapy to metastases of the bone and brain. The patient passed away several months later from complications of coronary artery disease.

Case 2

Our service was consulted regarding a 63-year-old man with two masses in the ileum. Six months prior to coming to our attention he presented to an outside hospital complaining of bright red blood per rectum. His medical history was remarkable for RCC diagnosed 3 years prior and treated with a laparoscopic partial nephrectomy. He also had a history of a Gleason 6 prostate cancer treated with active surveillance. The pathology from his partial nephrectomy specimen demonstrated a 2.5-cm pT1a clear cell RCC (Fuhrman grade 3/4), with uninvolved margins. Accordingly, he was not recommended to have any adjuvant systemic therapy.

At the time of presentation to the outside hospital, he received two units of packed RBCs and underwent upper and lower endoscopies that were unremarkable. He was followed by his primary care physician and found to have a persistently decreased hematocrit level and hemoccult-positive stools. During this time, he remained asymptomatic and hemodynamically stable. Video capsule enterography revealed two masses within the terminal ileum. A CT scan revealed two well-circumscribed, enhancing masses within the ileum, the largest of which was 4 cm (Fig. 3). Our service was consulted, and we elected to proceed with operative management.

Via a short midline laparotomy, we eviscerated and carefully examined the entire small bowel. Two masses were found within a 15-cm segment of the ileum, and this segment was resected and a stapled side-to-side anastomosis was performed. The patient's post-operative course was uncomplicated, and he was discharged to home on post-operative day 3. Final pathology demonstrated two small

Fig. 3 Computed tomography (CT) scan of the abdomen and pelvis showing two contrast-enhancing masses in the ileum

bowel masses measuring 5.5 and 2.5 cm in size, both of which were histologically consistent with metastatic clear cell renal cell carcinoma. The patient has not been treated with any systemic therapy and has had no further GI bleeding. He is being monitored with surveillance imaging every 6 months.

Case 3

A 59-year-old female presented to our Emergency Department with a headache, emesis, and bloody diarrhea. She had a history of metastatic RCC that initially came to attention 5 years prior. She underwent a left nephrectomy with pathology demonstrating a 7.5-cm pT2 clear cell RCC (Fuhrman grade 2–3/4), with negative resection margins. Over the ensuing year, she had multiple CT scans demonstrating metastatic disease to the lungs, and she underwent right upper lobe, right lower lobe, and left upper lobe wedge resections as well as a right upper lung lobectomy. Six months prior to her presentation to us, she developed new-onset headaches, visual spots, nausea, and tingling in her right hand, and an MRI revealed enhancing masses in the left occipital and left parietal lobes concerning for brain metastases. She had since been undergoing radiation treatment to these metastatic lesions, but she was not receiving systemic therapy of any kind.

Upon admission, she was found to have a hemoglobin level of 9.3 g/dL, decreased from 13.1 g/dL 3 weeks prior. She was admitted to the medical oncology service and underwent an unrevealing esophagogastroduodenoscopy and colonoscopy. Subsequent nuclear-tagged RBC scan suggested a focus of bleeding in the proximal jejunum. The Interventional Radiology service performed mesenteric

Fig. 4 Gross photograph of metastatic RCC to a segment of jejunum

angiography and found a focal area of hyperemia in the proximal jejunum that corresponded to the area of localization on the tagged RBC scan. The area could not be embolized due to concern for ischemic perforation but was thought to represent a tumor blush. Three days after admission, the surgical oncology team was consulted for operative management, and we proceeded with an exploratory laparotomy.

In the operating room, we carefully examined the entire small bowel and identified a single lesion in the proximal jejunum that measured 2 cm in diameter. The lesion was grossly ulcerated with a central hemorrhagic area (Fig. 4). A small segment of jejunum containing the mass was resected and a stapled side-to-side anastomosis performed. The patient's post-operative course was uncomplicated, and she was discharged to home on post-operative day 2. Final pathology demonstrated a dome-shaped, centrally ulcerated 1.1-cm mass consistent with metastatic clear cell RCC, and the margins of resection were negative. Since discharge, the patient has had no further GI bleeding and her hemoglobin levels have normalized, but she has had multiple readmissions for increasing lower extremity weakness thought to be secondary to her brain metastases. She was started on pembrolizumab 2 months after this episode of GI bleeding.

Discussion

GI bleeding is a common medical emergency associated with significant morbidity and mortality. Hemorrhage is the most common gastrointestinal cause of hospitalization, with over 500,000 cases in the United States in 2012 [7]. It is often difficult to determine the source of bleeding, as though bright red blood per rectum most commonly indicates a lower gastrointestinal source, it can also be present in the case of a brisk upper GI bleed (UGIB). Malignancy is a rare

Table 1 Case reports of metastatic RCC to the small bowel since 2015

Case report	No. of Patients	Presentation
Vani et al., <i>J Clin Diagn Res.</i> April 2017	2	Intussusception
Salamah et al., <i>J Coll Physicians Surg Pak.</i> April 2017	1	GI bleeding
Medic et al. <i>Urol Case Rep.</i> April 2017	1	Obstructive symptoms
Bellio et al. <i>J Med Case Rep.</i> Aug 2017	1	Intussusception
Jideh et al., <i>Gastrointes Endos.</i> May 2016	1	Biliary obstruction/jaundice
Shibutani et al., <i>Gan To Kagaku Ryoho.</i> Nov 2015	1	GI bleeding
Cannistra et al. <i>Ann Ital Chir.</i> Dec 2015	1	GI bleeding and obstruction
Ismali et al. <i>BMJ Case Rep.</i> Sep 2015	1	Obstructive symptoms
Mishra et al., <i>Indian J Surg.</i> Feb 2015	1	Intussusception
Massy Budmiger et al., <i>J Surg Case Rep.</i> April 2015	1	Intussusception
Gonski et al., <i>Int J Surg Case Rep.</i> Aug 2015	1	GI bleeding

cause of UGIB, estimated to account for 2–8% of cases, with peptic ulcer disease, variceal hemorrhage, erosive disease, esophagitis, and Mallory–Weiss tears all thought to be much more common [8]. The sources of UGIB in cancer patients are much different than those in the general population. In a retrospective cohort study of cancer patients with UGIB, tumor represented the source of bleeding in 84% of patients with known GI tract tumors. Among patients with known tumors outside of the GI tract, although the most common causes of UGIB mirrored those of the general population, metastatic disease was identified as the source of bleeding in nearly 11% [9]. For lower GI bleeding, small bowel diseases, such as Crohn's ileitis, Meckel's diverticula, tumors, and vascular ectasia, represent the cause of bleeding in only 2–9% of cases [10].

Tumors of the small intestine, both benign and malignant, are rare and represent just 3% of all tumors of the gastrointestinal tract [11]. Approximately half of small bowel tumors are metastases, with the ileum being the most common location. In a retrospective review of 44 patients with metastatic small bowel tumors, colon cancer was the most common primary, identified in 43.2% of cases, followed by pancreatic cancer and ovarian cancer each in 11.4% of cases, lung cancer in 9.1% of cases, and melanoma in 6.8% of cases. RCC represented the primary site in just two cases (4.5%) [12]. Similarly, autopsy studies demonstrate that only 2% of tumors metastasize to the small bowel, with 7.1% of these lesions being metastatic RCC [13].

RCC can cause GI bleeding via direct invasion or via metastatic disease. Metastatic RCC to the small bowel can also present as a small bowel intussusception or obstruction.

Our three case reports highlight the importance of considering metastatic disease as a source of bleeding in patients with a known history of RCC who present with GI bleeding. Although individual case reports claim that metastatic RCC to the small bowel is exceedingly rare, the number of published case reports in the literature may suggest

otherwise. A literature search using the PubMed search criteria “metastatic AND RCC OR renal cell carcinoma AND small bowel” identified 11 published case reports or case series of 12 different patients with symptomatic, metastatic RCC to the small bowel since 2015. Of these 12 cases, 5 patients presented with intussusception, 3 with GI bleeding alone, 2 with bowel obstruction, 1 with biliary obstruction, and 1 with both GI bleeding and bowel obstruction (Table 1). Additionally, using the same search criteria, since 2000, there have been 46 published cases of symptomatic, metastatic RCC to the small bowel, including 4 cases published between 2000 and 2005, 11 between 2006 and 2010, 25 between 2011 and 2015, and 6 so far since 2016. This number almost certainly represents only a small proportion of the total number of cases.

One possible explanation for the increased number of published cases of metastatic RCC to the small bowel in recent years is increased survival due to a revolution in targeted chemotherapeutics in the last decade. For example, several agents targeting the vascular endothelial growth factor (VEGF pathway) or the mammalian target of rapamycin (mTOR) pathway have become the standard of care in patients with advanced RCC, improving the median overall survival in these patients from approximately 12 months in the cytokine era of treatment to more than 26 months with first-line VEGF inhibitors [14]. As these patients live longer it is possible their primary tumors have more time to metastasize to the small bowel and become symptomatic.

The actual prevalence of metastatic RCC to the small bowel is largely unknown. One cohort study of 3,637 patients with RCC identified 26 patients (0.71%) with pathologically proven RCC metastases to the GI tract [15]. However, this number only represents symptomatic cases that came to medical attention and had tissue confirmation and thus likely underestimates the true prevalence of disease. This same study demonstrated that the most common clinical presentation of metastatic RCC to the small bowel was

GI bleeding, found in 67% of cases. Though RCC metastases to the small bowel are most commonly seen in the setting of more widespread metastatic disease to other sites, since 2015, there have been at least four published reports of isolated RCC metastases to the small bowel [2, 6, 16, 17]. Of particular interest is the report by Ismaili et al. [6], which describes a patient with a T1a tumor treated with a radical nephrectomy 20 years prior who developed a solitary jejunal metastasis, as this case is quite similar to our case #2 presented herein.

Metastatic RCC to the small bowel disease may be more common than previously thought, and we emphasize that it should be strongly considered in patients with a known history of RCC who present with GI bleeding.

Compliance with ethical standards

Conflict of interest The authors declare that no conflicts of interest exist.

Human and animal rights This retrospective chart review study involving human participants was conducted in accordance with the ethical standards of the institutional research committee at MGH (IRB approval # 2008P000578).

Informed consent According to our IRB committee, informed consent from all participants included in this study was not required given the fact that all included patient data and images are de-identified, and thus the study was deemed to be of minimal risk to the participants.

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